

function associated with the specific proteins encoded by the claimed nucleic acids or any disease states directly related to its dysfunction. The Examiner also asserts that the specification does not disclose any instances where disorders can be effected by interfering with the activity of the claimed nucleic acids. The Examiner alleges that the corresponding utilities of the claimed nucleic acids are limited to identifying other nucleic acids that hybridize to said polynucleotides, identifying disease states associated with polypeptide dysfunction or targeting drugs for discovery. According to the Examiner, these asserted utilities are the only utilities known for the claimed nucleic acids and are not sufficient as required by the United States Patent Laws. Applicants respectfully traverse. With this amendment, Applicants attach an expert declaration under 37 C.F.R. § 1.132 by Dr. Timothy Jegla explaining that, at the time of the invention, one of skill in the art would easily recognize a “substantial” or “real world” utility for the claimed nucleic acids. In fact, one of skill in the art, after reading the specification, would believe that the claimed nucleic acids play a significant role in sperm capacitation.

Introduction

According to the MPEP, in order to assess utility, the Examiner should review the specification to determine if there are any statements asserting that the claimed invention is useful for any particular purpose. An invention has utility if the utility is specific, substantial and credible. A utility is specific if it is specific to the subject matter claimed. A utility is substantial if it has a real-world use. In most cases, an applicant’s assertion of utility creates a presumption of utility that is sufficient to satisfy the utility requirement of 35 U.S.C. § 101. Furthermore, an Examiner cannot simply dismiss an assertion of a particular utility as wrong but must determine if the assertion is credible, i.e., would be believable to a person of ordinary skill in the art based on the totality of the evidence. (See MPEP 2107.02).

A *prima facie* showing of lack of utility must establish that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the applicant would be specific and substantial. The present application claims isolated nucleic acid and amino acid sequences of a Slo3 potassium channel expressed in spermatocytes that is activated by changes in intracellular pH and membrane potential. At the time the application was filed, one of skill in the art would recognize the utility of Slo3 potassium channels expressed in spermatocytes. In order to demonstrate that one of skill in the art would recognize the utility of the present invention and appreciate its real world context, Applicants have included a declaration by Dr. Timothy Jegla, Chief Scientist at ICAGEN, Inc.

Declaration of Dr. Timothy Jegla

In his declaration, Dr. Jegla explains why one of skill in the art would recognize the utility of the present invention. Dr. Jegla's resume is attached hereto as Exhibit C. According to Dr. Jegla, it is well known in the art that intracellular pH has a profound effect on the viability of mammalian sperm. Applicants submit Exhibits A and B, two references that disclose that alkaline pH is necessary for sperm capacitation and the acrosome reaction. Sperm capacitation is known to be accompanied by increases in potassium permeability that hyperpolarizes the membrane. According to Dr. Jegla, because the newly identified Slo3 is highly and specifically expressed in sperm and is activated by alkalization, persons of skill in the art would expect that the Slo3 channel plays an important role in sperm capacitation, e.g., by increasing potassium permeability. In fact, according to Dr. Jegla, after reading the present application, persons of skill in the art would expect that Slo3 is an excellent target for candidate compounds that modulate sperm function. Assays for such compounds, using Slo3 as a target, are useful for identifying compounds that affect fertility. For example, persons of skill in the art would expect that Slo3 openers could be used to initiate the capacitation cascade. A Slo3 opener, therefore, could be used to treat certain types of infertility caused by reduced sperm function. Persons of skill in the art would also expect that Slo3 blockers could

inhibit or block capacitation and the acrosome reaction. A person of skill in the art would expect that a Slo3 blocker, for example, could be useful as a contraceptive device.

The nucleic acids of this invention have specific, substantial and credible utility

As noted by the Examiner in the present Office Action, Applicants have shown that the claimed nucleic acids encode a full length monomer of a pH sensitive potassium channel, the monomer having a unit conductance of approximately 80-120 pS when in functional tetrameric form. It is also noted that the monomer is capable of transporting potassium ions, has increased potassium ion transporting activity above an intracellular pH of 7.1, and specifically binds to polyclonal antibodies generated against a polypeptide comprising an amino acid sequence of the disclosed SEQ ID NOs. Applicants submit that as well as characterizing the functional characteristics of the claimed nucleic acids, they have disclosed a "substantial" use for them in the specification.

On page 2 of the specification, lines 22-35, Applicants explain that cellular signaling in spermatoc cells is tightly regulated to prevent inappropriate activation of the irreversible steps that prepare the sperm to fertilize the oocyte. As evidenced by Exhibits A and B, it is known in the art that these essential steps of fertilization are triggered and coordinated by changes in membrane potential, intracellular calcium concentration, and pH level. Between mating and fertilization, sperm undergo capacitation, a process which enables them to penetrate and fertilize an egg. The nucleic acids of this invention encode a potassium channel that opens and closes depending upon the changes in intracellular pH and membrane potential in spermatocytes. Persons of skill in the art would expect that this opening and closing of the channel is necessary for maintaining the conditions essential for capacitation. Without proper capacitation, fertilization cannot occur.

On page 3, line 15 of the specification, Applicants disclose that the nucleic acids of their invention are regulated by pH levels and are abundantly expressed in spermatocytes. Figures 2A-D demonstrate that expression of the mouse Slo3 transcripts is largely restricted to the testis. On page 12 of the specification, lines 21-34, it is disclosed that spermatocytes that lack Slo3 expression may lack the capability of undergoing capacitation or acrosome reactions. Finally, on page 48 of the specification, lines 30-33, Applicants disclose that modulators of the Slo3 channel may be used to treat infertility conditions due to Slo3's involvement in capacitation and the acrosome reaction.

In the present Office Action, the Examiner alleges that there are no disclosed disease states directed related to Slo3 dysfunction. Applicants respectfully traverse. Infertility is a condition that negatively affects millions of men and women in this country. An extraordinary amount of money and resources is used to treat infertile couples and to fund fertility research. Applicants have shown that persons of skill would believe that Slo3 plays a role in fertilization. This application, therefore, has disclosed a credible, specific, and substantial utility for the claimed nucleic acids.

The declaration by Dr. Jegla, in particular, is evidence that the nucleic acids of this invention have a substantial utility. As mentioned above, the nucleic acids of the present invention encode a Slo3 protein channel that is predominantly expressed in spermatocytes and that is regulated by pH levels and changes in membrane potential therein. The application was filed because those of skill in the art believe that Slo3 channels are excellent targets for modulation of sperm function and thereby have a substantial utility.

Dr. Jegla, however, is not the only scientist that believes that potassium channels expressed predominantly in spermatocytes play an important role in fertility. Slo3 channels were discovered by scientists at ICAGEN, Inc. ICAGEN, Inc. is a privately

held company engaged in pharmaceutical discovery and development, focusing exclusively on ion channels as drug targets. ICAGEN scientists and investors alike recognize that compounds that increase or decrease the flow of ions by selectively opening or blocking specific channels can aid in the treatment of many diseases. ICAGEN, Inc. was formed based on the belief that ion channels play crucial roles in all functions and pathophysiological processes in the human body. Therefore, the scientists at ICAGEN understand the importance and utility of nucleic acids that encode newly discovered potassium channels. Scientists at ICAGEN, Inc. believe that the newly discovered and characterized Slo potassium channel is particularly important because it is expressed in spermatocytes and is pH sensitive.

Fertility is a multi-million dollar industry. The cloning of a potassium channel that regulates the process of sperm capacitation has extraordinary implications for fertility treatment. Slo3 channel openers and blockers can be manipulated to either treat infertility or to prevent fertilization depending upon the needs of a patient. A "substantial utility" defines a "real world" use. Clearly, treating fertility is a real world use thereby indicating that the nucleic acids of this invention have a substantial as well as a specific utility.

Finally, the utility of the claimed nucleic acids is credible. Based on the totality of the evidence, one of skill in the art would believe that the channels encoded by these nucleic acids play a role in sperm capacitation. Therefore, the nucleic acids of the present invention are specific, substantial and credible and thus fulfill the requirements of 35 U.S.C. §101.

The nucleic acids of the invention have a well established utility

Assuming *arguendo*, that Applicants neglected to assert a specific, substantial and credible utility in the application, the Examiner should find that, after reading this application, one of skill in the art would immediately appreciate why the

invention is useful based on the characteristics of the invention. As explained in the attached declaration, it is well-known that intracellular pH has a profound effect on the viability of mammalian sperm and that alkaline pH is necessary for sperm capacitation and the acrosome reaction. Furthermore, sperm capacitation is known to be accompanied by increases in potassium permeability that hyperpolarize the membrane. This membrane potential is thought to be critical for increasing the driving force for calcium entry, a critical step in the capacitation process. Anyone of skill in the art would recognize that because Slo3 is highly expressed in sperm and is activated by alkalization, it is an excellent target for the modulation of sperm function. One of skill in the art would realize that by modulating sperm function, it is possible to affect the capacitation process in sperm and to thereby treat fertility. Therefore, it is well-established that a pH sensitive channel expressed predominantly in spermatocytes would be immediately appreciated by one of skill the art. The Examiner should find that the nucleic acids of the present invention have a well-established utility.

With these remarks, the Applicants have demonstrated that their invention has a specific, substantial, credible and well-established utility. The Examiner should not find otherwise. Accordingly, this application meets the requirements of 35 U.S.C. § 101.

CONCLUSION

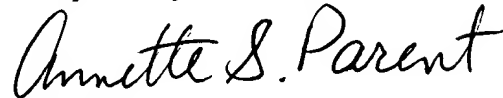
In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

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PATENT

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

A handwritten signature in cursive script that reads "Annette S. Parent".

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APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (thrice amended) An isolated nucleic acid encoding a polypeptide monomer of a pH sensitive potassium channel, the monomer:

(i) forming a potassium channel having a unit conductance of approximately 80-120 pS and having increased potassium channel current activity above approximately intracellular pH of 7.1, when the monomer is expressed in a *Xenopus* oocyte; and

(ii) [specifically binding to polyclonal antibodies generated against an amino acid sequence of SEQ ID NO:1, SEQ ID NO:16, or SEQ ID NO:18] encoded by a nucleic acid that selectively hybridizes under moderate stringency hybridization conditions to a nucleic acid comprising a nucleotide sequence of SEQ ID NO:2, 16, or 18, wherein the hybridization reaction is incubated at 37°C in a solution comprising 40% formamide, 1 M NaCl, and 1% SDS and washed at 45°C in a solution comprising 1x SSC.